REMARKS

As now claimed, the present invention provides methods for selecting a therapy for a subject suffering from schizophrenia, determining whether an MTHFR mutation is indicative of a response to a therapy for schizophrenia, or preventing, delaying, or treating schizophrenia in a subject by selecting and administering a therapy based on the presence of a heterozygous C/T mutation at position 677 of MTHFR in the subject.

Claims 29-52 were examined in this case. All of these claims were rejected under 35 U.S.C. § 112, first and second paragraphs, and under 35 U.S.C. § 103(a). Claims 29-33, 37-41, and 45-49 were further rejected under 35 U.S.C. § 102. Each of these rejections is addressed below in the order that it appears in the Office Action.

Support for the Amendments

Applicant has amended claims 29, 37, and 45 to indicate that the claimed psychosis is schizophrenia and that the MTHFR mutation referred to in the claims is the heterozygous C/T mutation at position 677 (as disclosed, for example, at page 18, lines 6 and 7, and pages 80-82). Claim 29 was amended to clarify that the method includes the step of selecting a safe or efficacious therapy for a subject that has a heterozygous 677 C/T MTHFR mutation that is indicative of the safety or efficacy of the therapy, and claim 37 was amended to clarify that the MTHFR mutation is indicative of the safety or efficacy of the therapy (as disclosed, for example, on page 14, lines 3-25, and page 22, lines 9-29). Amended claim 45 specifies that a preferred therapy is efficacious, safe,

and/or has reduced toxicity compared to another therapy for schizophrenia, and amended claims 34, 42, and 50 specify that the subject is determined to have two MTHFR mutations at a position other than 677 (as disclosed, for example, on page 18, lines 1-5, and page 22, lines 9-29).

A marked-up version indicating the amendments made to the specification and claims, as required by 37 C.F.R. § 1.121(b)(1)(iii) and (c)(1)(ii), is enclosed. These amendments add no new matter.

Objection to the Title

The Examiner states that the title of the application is not descriptive. As suggested by the Examiner, Applicant has replaced the title with the following description of the claimed subject matter: "Methods for Selecting a Therapy for a Subject Suffering from a Schizophrenia."

Rejections under 35 U.S.C. § 112, first paragraph

Claims 29-52 stand rejected, under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Office acknowledges that the specification is enabling for methods for detecting the presence of a C to T mutation at position 677 of the MTHFR gene (i) to identify subjects in need of therapy for schizophrenia, (ii) to identify subjects with schizophrenia that have an increased likelihood of responding to neuroleptic therapy, and (iii) to treat subjects with this mutation by administration of a neuroleptic medication.

However, the Office asserts that the specification "does not reasonably provide enablement for methods of selecting a therapy for a subject suffering from any type of psychosis wherein the methods detect any mutation in the MTHFR gene or for research methods which determine whether a mutant MTHFR allele is associated with the safety or efficacy of a type of treatment for psychosis."

In response to the assertion that the specification does not enable diagnostic methods for psychoses in general, Applicant notes that, in the interest of expediting prosecution, claims 29 (from which claims 30-36 and 53 depend), 37 (from which claims 38-44 and 54 depend), and 45 (from which claims 46-52 and 55 depend) have been amended to indicate that the psychosis is schizophrenia. For the record, Applicant does not agree with the present rejection and reserves the right to pursue the canceled subject matter in this or a related continuing application. This aspect of the rejection is now moot.

Regarding the second basis for this rejection - that the specification is not enabling for methods involving mutations other than 677 C/T, claims 29, 37, and 45 have also been amended in the interest of expediting prosecution to specify that the MTHFR mutation referred to in the claims is a heterozygous C/T mutation at position 677. As noted by the Examiner, Applicant's specification demonstrates an association between this heterozygous 677C/T mutation and schizophrenia (see, for example, pages 79-82). For example, the specification teaches:

> [w]e have discovered that the heterozygous form of the C677T mutation in methylenetetrahydrofolate reductase (MTHFR) is more common in patients diagnosed with schizophrenia than in a healthy control population and thus is a risk factor for this disease. In addition, both the heterozygous and homozygous forms of this mutation are associated with an improved response to neuroleptic treatment and long-term outcome. (page 79, lines 3-10)

Based on Applicant's specification, a skilled artisan can readily select a therapy for a schizophrenic subject that has a heterozygous 677C/T MTHFR mutation, determine whether the heterozygous 677C/T MTHFR mutation is indicative of a response to a therapy for schizophrenia, or select and administer a preferred therapy to a subject that has a heterozygous 677C/T MTHFR mutation for the prevention or treatment of schizophrenia (see, for example, pages 12-15 and 84-87).

Because the specification provides sufficient guidance and working examples for these methods, no undue experimentation is required to practice the claimed invention, and this rejection under § 112, first paragraph, should be withdrawn.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 29-52 stand further rejected, under 35 U.S.C. § 112, second paragraph, as being indefinite.

In particular, claims 29-36 were rejected (i) for failure to establish a relationship between selecting a therapy and detecting an allele that is indicative of safety or efficacy and (ii) for failure to indicate whether the recited methods involve selection of therapies in general or selection of therapies that are safe or efficacious. Claim 29 (from which

claims 30-36 depend) has been amended to clarify that the method includes the step of selecting a safe or efficacious therapy for a subject based on the presence of a heterozygous 677 C/T MTHFR mutation that is indicative of the safety or efficacy of the therapy. Accordingly, this aspect of the rejection may be withdrawn.

Claims 37-44 were rejected for failure to indicate whether the MTHFR mutation is indicate of a response to a therapy or indicative of the safety or efficacy of the therapy. As claim 37 (from which claims 38-44 depend) has been amended to clarify that the MTHFR mutation is indicative of the safety or efficacy of the therapy, this aspect of the rejection may be withdrawn.

The Examiner states that claims 34, 35, 42-44, and 50-52 are indefinite for use of the phrase "subject comprises at least two MTHFR mutant alleles." Claims 34 (from which claim 35 depends), 42 (from which claims 43 and 44 depend), and 50 (from which claims 51 and 52 depend) have been amended to specify that the subject is determined to have two MTHFR mutations at a position other than 677. This aspect of the rejection may be withdrawn.

Claims 45-52 were rejected for their alleged failure to specify the criteria for determining a "preferred therapy." As claim 45 (from which claims 46-52 depend) has been amended to specify that a preferred therapy is efficacious, safe, and/or has reduced toxicity compared to another therapy for schizophrenia (as disclosed, for example, on page 22, lines 9-29), the final aspect of this rejection may be withdrawn.

Rejections under 35 U.S.C. § 102(a)

Claims 29-33 and 37-41 stand further rejected, under 35 U.S.C. § 102(a), as being anticipated by Joober *et al.* Molecular Psychiatry 5:323-326, May 2000. This rejection is respectfully traversed. As stated by Ms. Gillian Riley, the Production Controller for Nature Publishing Group in the enclosed Exhibit A, the May 2000 issue of Molecular Psychiatry containing the Joober reference was first released on June 15, 2000. As the publication date of the Joober reference is after the June 12, 2000 filing date of the present application, Joober does not constitute prior art to the present invention. This rejection should be withdrawn.

Claims 29-33 and 37-41 also stand rejected, under 35 U.S.C. § 102(a), as being anticipated by another Joober *et al.* reference (Molecular Psychiatry 4:S15-S16, 1999). In response to this rejection, a Declaration from Dr. Rima Rozen is filed herewith. This Declaration states that any description of the present invention in this Joober reference was the inventive contribution of inventor, Rima Rozen alone, notwithstanding the inclusion of additional authors on this reference. In view of this Declaration, and because the Joober reference was published within one year of the present filing date, this reference does not constitute prior art to the present invention, and the rejection may be withdrawn.

Claims 29-33 stand further rejected, under 35 U.S.C. § 102(a), as being anticipated by Arinami (American Journal of Medical Genetics 74:526-528, 1997). In particular, the

Examiner states that Arinami teaches the association of the **homozygous** C677T mutation and schizophrenia. This rejection is respectfully traversed.

Applicant's discovery that the heterozygous form of the C677T MTHFR mutation is more common in patients diagnosed with schizophrenia than in a healthy control population led to the now claimed methods for selecting a safe or efficacious therapy for a subject with schizophrenia based on a **heterozygous** C677T MTHFR mutation. Nowhere is such a therapy selection method disclosed or suggested by the Arinami reference. This rejection should be withdrawn.

Claims 29-33, 37-41, and 45-49 stand further rejected, under 35 U.S.C. § 102(a), as being anticipated by Regland *et al.* (Journal of Neural Transmission 104:931-941, 1997). This rejection is also respectfully traversed.

As noted above, the present claims have been amended to specify that the MTHFR mutation referred to in the claims is a **heterozygous** C677T mutation. Regland does not disclose or suggest methods either for determining the presence of a heterozygous C677T MTHFR mutation in a subject in order to select a therapy for that subject to treat schizophrenia, for determining whether the MTHFR mutation is indicative of a response to a therapy for schizophrenia, or for preventing or treating schizophrenia in the subject, as required by the present claims.

Specifically, Regland teaches that in a population of patients that were selected based on the presence of a schizophrenia-like disorder and hyperhomocysteinemic serum levels, the homozygous form of the C677T MTHFR mutation was found with high

frequency (7 out of 11 patients). From these experiments, Regland concludes that the **homozygous** form of this mutation, which is associated with hyperhomocysteinemia, is a risk factor for schizophrenia. Regland does not teach or suggest that the **heterozygous** form of the C677T MTHFR mutation is more common in schizophrenia patients than control patients, or is associated with increased risk for schizophrenia. Neither does Regland make any association between the heterozygous C677T mutation and schizophrenia treatment selection or response. In view of these clarifying remarks, this rejection may be withdrawn.

Rejections under 35 U.S.C. § 103(a)

Claims 29-52 stand further rejected, under 35 U.S.C. § 103(a), as being unpatentable over Joober (2000) or Joober (1999). As noted above, these references do not constitute prior art to the present invention. These rejections may be withdrawn.

Claims 29-33 also stand rejected, under 35 U.S.C. § 103(a), as being obvious in view of Arinami. The Examiner states that, given the association of the **homozygous** C677T mutation and schizophrenia, it would have been obvious to identify a subject requiring treatment for schizophrenia, to select a therapy for a subject suffering from schizophrenia, or to treat a subject with schizophrenia based on the presence of the C677T mutation in the subject. Applicant respectfully disagrees.

No only does Arinami fail to detect an association between the heterozygous C677T mutation and schizophrenia, Arinami reports that the **heterozygous** C677T

mutation is **less** common in patients diagnosed with schizophrenia than in control patients (46 versus 51%; Table 1). Arinami further states that "[s]ince **only homozygotes** for T677 have mild MTHFR deficiency and mild hyperhomocysteinemia, our analysis involves the associations between psychiatric disorders and the homozygous state for the T677 variant" (paragraph bridging pages 526 and 527; emphasis added). The failure of Arinami to detect an association between the **heterozygous** C677T mutation and schizophrenia is contrary to Applicant's discovery of such an association and teaches away from the present invention. As stated by the Court of Appeals for the Federal Circuit in *Stratoflex, Inc. v. Aeroquip Corp.*, "evidence rising out of the so-called 'secondary considerations' must always when present be considered en route to a determination of obviousness" [713 F.2d 1530, 1538, 218, USPQ 871, 879 (Fed. Cir. 1983)]. Similarly, MPEP § 2141 states that

> [o]bjective evidence or secondary considerations such as unexpected results, commercial success, long-felt need, *failure of others*, copying of others, licensing, and skepticism of others, copying by others, licensing, and skepticism of experts are relevant to the issue of obviousness and must be considered in every case in which they are present. (emphasis added)

Additionally, a reference that teaches away from the invention cannot render the invention obvious. *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1599 (Fed. Cir. 1988).

In view of these clarifying remarks, the obviousness rejection based on Arinami should be withdrawn.

Claims 29-52 stand further rejected, under 35 U.S.C. § 103(a), as being anticipated by Regland. This rejection is also respectfully traversed.

This teaching of Regland also would not lead one skilled in the art to arrive at Applicant's invention, nor would it provide a reasonable expectation of success for Applicant's therapy selection and treatment methods based on a **heterozygous** C677T mutation. Although Regland concludes that the **homozygous** form of this mutation, which is associated with hyperhomocysteinemia, is a risk factor for schizophrenia, Regland does not teach or suggest that the **heterozygous** form of the C677T MTHFR mutation is associated with increased risk for schizophrenia or is indicative of repsonse to a therapy for schizophrenia. In particular, a skilled artisan would have expected the heterozygous C677T MTHFR mutation to lead to a much smaller reduction in MTHFR enzymatic activity and a much smaller increase in homocysteine levels than the homozygous mutation. Thus, prior to the present invention, it was highly unpredictable whether heterozygous mutations, such as the C677T mutation, would be risk factors for schizophrenia.

Conclusion

On the basis of the foregoing amendments and remarks, Applicant respectfully submits that pending claims 29, 31-37, 39-45, and 47-52 are in condition for allowance, and a Notice of Allowance is respectfully requested.

If there are any charges, or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: July 24, 2003

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Rima Rozen	Art Unit:	1634
Serial No.:	09/931,795	Examiner:	Carla J. Myers
Filed:	August 16, 2001	Customer No.:	21559
Title:	METHODS FOR SELECTING A THERAPY FOR A SUBJECT SUFFERING FROM SCHIZOPHRENIA (Amended)		

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Version with Markings to Show Changes Made

In the specification:

A marked-up version of the title on page 1, lines 1 and 2, of the specification is shown below.

Methods for Selecting a Therapy for a Subject Suffering from Schizophrenia

[cDNA FOR HUMAN METHYLENETETRAHYDROFOLATE REDUCTASE AND USES THEREOF]

In the claims:

A marked-up version of claims 29, 31-37, 39-45, and 47-52 is shown below.

29. (Amended) A method for selecting a safe and/or efficacious therapy for a subject suffering from a schizophrenia [psychosis], said method comprising the steps of:

(a) analyzing the MTHFR nucleic acid in a sample obtained from said subject; [and]

(b) determining the presence of [at least one] a heterozygous C/T mutation at position 677 of MTHFR [mutant allele] in said subject, wherein the presence of said mutation [mutant allele] is indicative of the safety or efficacy of a therapy; and

(c) selecting a safe or efficacious therapy for said subject.

31. (Amended) The method of claim 29, wherein said nucleic acid with said mutation at position 677 [said mutant allele] encodes an MTHFR protein with reduced activity or reduced thermal stability.

32. (Amended) The method of claim 29, wherein said nucleic acid with said mutation at position 677 further [said mutant allele] comprises a G/A mutation at position 167, a G/A mutation at position 482, a C/T mutation a position 559, [a C/T mutation at position 677,] a C/T mutation at position 692, a C/T mutation at position 764, a G/A mutation at position 792+1, a C/T mutation at position 985, a C/T mutation at position

1015, a C/T mutation at position 1081, an A/C mutation at position 1298, or a T/C mutation at position 1317.

33. (Amended) The method of claim 32, wherein said nucleic acid with said mutation at position 677 [said mutant allele] comprises [a C/T mutation at position 677 or] an A/C mutation at position 1298.

34. (Amended) The method of claim 29, wherein said subject is determined to comprise [comprises] at least two MTHFR mutations at a position other than 677 [mutant alleles].

35. (Amended) The method of claim 34, wherein said mutations at a position other than 677 [said mutant alleles] comprise at least one of a G/A mutation at position 167, a G/A mutation at position 482, a C/T mutation a position 559, [a C/T mutation at position 677,] a C/T mutation at position 692, a C/T mutation at position 764, a G/A mutation at position 792+1, a C/T mutation at position 985, a C/T mutation at position 1015, a C/T mutation at position 1081, an A/C mutation at position 1298, or a T/C mutation at position 1317.

36. (Amended) The method of claim 35, wherein said mutations at a position other than 677 [said mutant alleles] comprise [at least one of a C/T mutation at position 677 or] an A/C mutation at position 1298.

37. (Amended) A method for determining whether an MTHFR mutation [a mutant allele] is indicative of the safety or efficacy of [a response to] a therapy for a schizophrenia [psychosis], said method comprising [comprises] the steps of:

(a) determining whether said response of a first subject or set of subjects at increased risk for or diagnosed with said schizophrenia [psychosis] differs from said response of a second subject or set of subjects at increased risk for or diagnosed with said schizophrenia [psychosis];

(b) analyzing the MTHFR nucleic acid in a sample obtained from said first subject or set of subjects and said second subject or set of subjects; and

(c) determining whether [at least one] a heterozygous C/T mutation at position 677 of MTHFR [mutant allele] differs between said first subject or set of subjects and said second subject or set of subjects, wherein the presence of said mutation [mutant allele] is correlated to the safety or efficacy of said therapy [said response], thereby determining whether said mutation [mutant allele] is indicative of the safety or efficacy of said therapy.

39. (Amended) The method of claim 37, wherein said nucleic acid with said mutation at position 677 [said mutant allele] encodes an MTHFR protein with reduced activity or reduced thermal stability.

40. (Amended) The method of claim 37, wherein said nucleic acid with said mutation at position 677 further [said mutant allele] comprises a G/A mutation at position 167, a G/A mutation at position 482, a C/T mutation a position 559, [a C/T mutation at position 677,] a C/T mutation at position 692, a C/T mutation at position 764, a G/A mutation at position 792+1, a C/T mutation at position 985, a C/T mutation at position 1015, a C/T mutation at position 1081, an A/C mutation at position 1298, or a T/C mutation at position 1317.

41. (Amended) The method of claim 40, wherein said nucleic acid with said mutation at position 677 [said mutant allele] comprises [a C/T mutation at position 677 or] an A/C mutation at position 1298.

42. (Amended) The method of claim 37, wherein said subject is determined to comprise [comprises] at least two mutations at a position other than 677 [mutant alleles].

43. (Amended) The method of claim 42, wherein said mutations at a position other than 677 [said mutant alleles] comprise at least one of a G/A mutation at position 167, a G/A mutation at position 482, a C/T mutation a position 559, [a C/T mutation at position 677,] a C/T mutation at position 692, a C/T mutation at position 764, a G/A mutation at position 792+1, a C/T mutation at position 985, a C/T mutation at position 1015, a C/T mutation at position 1081, an A/C mutation at position 1298, or a T/C mutation at position 1317.

44. (Amended) The method of claim 43, wherein said mutations at a position other than 677 [said mutant alleles] comprise [at least one of a C/T mutation at position 677 or] an A/C mutation at position 1298.

45. (Amended) A method for preventing, delaying, or treating a schizophrenia [psychosis] in a subject, said method comprising the steps of:

(a) analyzing the MTHFR nucleic acid in a sample obtained from said subject;

(b) determining the presence of [at least one] a heterozygous C/T mutation at position 677 of MTHFR [mutant allele] in said subject, wherein the presence of said mutation [said mutant allele] is predictive of the safety or efficacy of at least one anti-psychotic therapy;

(c) determining a preferred therapy for said subject, wherein said preferred therapy is efficacious, safe, and/or has reduced toxicity compared to another therapy for schizophrenia; and

(d) administering said preferred therapy to said subject.

47. (Amended) The method of claim 45, wherein said nucleic acid with said mutation at position 677 [said mutant allele] encodes an MTHFR protein with reduced activity or reduced thermal stability.

48. (Amended) The method of claim 45, wherein said nucleic acid with said mutation at position 677 further [said mutant allele] comprises a G/A mutation at position 167, a G/A mutation at position 482, a C/T mutation a position 559, [a C/T mutation at position 677,] a C/T mutation at position 692, a C/T mutation at position 764, a G/A mutation at position 792+1, a C/T mutation at position 985, a C/T mutation at position 1015, a C/T mutation at position 1081, an A/C mutation at position 1298, or a T/C mutation at position 1317.

49. (Amended) The method of claim 48, wherein said nucleic acid with said mutation at position 677 [said mutant allele] comprises [a C/T mutation at position 677 or] an A/C mutation at position 1298.

50. (Amended) The method of claim 45, wherein said subject is determined to comprise [comprises] at least two mutations at a position other than 677 [mutant alleles].

51. (Amended) The method of claim 50, wherein said mutations at a position other than 677 [said mutant alleles] comprise at least one of a G/A mutation at position 167, a G/A mutation at position 482, a C/T mutation a position 559, [a C/T mutation at position 677,] a C/T mutation at position 692, a C/T mutation at position 764, a G/A mutation at position 792+1, a C/T mutation at position 985, a C/T mutation at position 1015, a C/T mutation at position 1081, an A/C mutation at position 1298, or a T/C mutation at position 1317.

52. (Amended) The method of claim 51, wherein said mutations at a position other than 677 [said mutant alleles] comprise [at least one of a C/T mutation at position 677 or] an A/C mutation at position 1298.

Add the following new claims 53-55.

53. (New) The method of claim 29, further comprising the step of determining the presence of at least one MTHFR mutation at a position other than 677 prior to step (c).

54. (New) The method of claim 37, further comprising determining whether at least one MTHFR mutation at a position other than 677 differs between said first subject or set of subjects and said second subject or set of subjects.

55. (New) The method of claim 45, further comprising determining the presence of at least one MTHFR mutation at a position other than 677 prior to step (c).